# 105. Metal Complexes with Macrocyclic Ligands

Part XL[1])

## Syntheses and Silver(I) Complexes of Mono- and Disubstituted Dithiadiazamacrocycles

by **Pascale C. Riesen** and **Thomas A. Kaden***

Institute of Inorganic Chemistry, Spitalstr. 51, CH–4056 Basel

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A series of $N_2S_2$-macrocycles with ring sizes varying between 12 and 16, as well as two 12-membered $N_2S_2$-rings with a pendant carboxylic and amino group, respectively, were synthesized. Their complexation properties towards $Ag^+$ were studied by pH titrations and by potentiometry with a silver electrode. The observation that 1:1 ($[AgLH_2]^{3+}$, $[AgLH]^{2+}$, $[AgL]^+$) and 1:2 species ($[AgL_2H_2]^{3+}$, $[AgL_2H]^{2+}$, $[AgL_2]^+$) were formed is interpreted by postulating that $Ag^+$ can bind either to the S-donors only, or to both the N- and S-atoms. The most stable complex $[AgL]^+$ in the series of the nonfunctionalized macrocycles was found for the 12-membered $N_2S_2$-ring **3**. The stability of it increased when an additional donor group was introduced into the side chain. The highest formation constant ($\log\beta_{110} = 14.43(1)$) was obtained with the 12-membered ring **12** carrying the ethanamine side chain. In view of a radiochemical application, all $Ag^+$ complexes were tested in blood serum for their stability, but were not stable enough against transmetallation.

**Introduction.** – Macrocyclic ligands with different donor atoms were developed and their complexation properties studied in detail [2]. That macrocycles with hard donors such as ether O-atoms or amino N-atoms mainly complex alkali or earth-alkali ions, whereas those with soft donors such as thioether S-atoms or phosphine P-atoms bind transition-metal ions, is well known, but for mono- and bicyclic ligands, several new properties were found in addition, such as selectivity [3], high thermodynamic stability (macrocyclic effect) [4], and kinetical inertness [5].

Especially because of the last two properties, the development and use of macrocyclic metal complexes in medicine has become possible [6] [7]. Several $Gd^{3+}$ complexes with tetraazacyclododecanes are used as contrast agents in magnetic-resonance imaging [6], and several radioactive isotopes were proposed to label monoclonal antibodies, modified by covalently attaching a macrocyclic unit to them, which can coordinate the radioactive metal ion [7]. For diagnostic purposes, one will choose radionuclides which are $\gamma$-emitters, such as $^{99m}Tc$, $^{111}In$, $^{67}Ga$, $^{131}I$, and $^{64}Cu$, whereas for therapeutic applications $\beta$-emitters, such as $^{67}Cu$, $^{90}Y$, $^{131}I$, $^{199}Au$, $^{111}Ag$, $^{188}Re$, and $^{161}Tb$, were proposed. $^{111}Ag$ ($T_{1/2}$ 179 h; $E_\beta = 1.04$, 0.69, 0.79 MeV; $E_\gamma = 342$, 247 keV) has ideal radiophysical properties for medical applications, but little has been done yet to label monoclonal antibodies with this isotope. This probably stems from the fact that $Ag^+$ is very labile, and in physiological liquids, there are many ligands which can compete with the macrocycle, and thus

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transmetallation can easily take place. To clarify the fundamental properties a macrocyclic ligand must have to give thermodynamically and kinetically stable $Ag^+$ complexes, we studied a series of macrocyclic ligands of different ring sizes with a $N_2S_2$-donor set and two 12-membered rings with an additional donor in the side chain. We describe here their synthesis and complexation properties towards $Ag^+$.

**Experimental.** – *General.* The starting compounds were either purchased or prepared according to the literature and characterized by m.p., IR, and NMR spectra: 2,2'-[(ethane-1,2-diyl)bis(thio)]bis[acetic acid] (**1**) [8] and 3,3'-[(propane-1,3-diyl)bis(thio)]bis[propanoic acid] **7** [9]. The 8-methyl-1,4-dithia-8,11-diazacyclotetradecane (**10**) was obtained from *E. Kamber* [10]. FC = flash chromatography. Melting points (m.p.): *Büchi-510* apparatus; uncorrected. IR Spectra: *Perkin-Elmer-1600* spectrophotometer; KBr pellets or films on NaCl plates. $^1$H- and $^{13}$C-NMR Spectra: *Varian-Gemini-300* or *-400* instrument; $\delta$ in ppm rel. to $SiMe_4$ as internal standard ( = 0 ppm). MS: spectrophotometer *VG 70-250;* FAB = fast-atom-bombardment ionization. Elemental analyses were performed by the analytical laboratory of *Ciba AG,* Basel.

*3,3'-[(Propane-1,3-diyl)bis(thio)]bis[acetic acid]* (**4**). To a soln. of NaOH (40 g, 1 mol) and 2-mercaptoacetic acid (46.06 g, 0.5 mol) in $H_2O$/EtOH 4:1 (500 ml), 1,3-dichloropropane (36.72 g, 0.325 mol) was added dropwise and the mixture was refluxed for 16 h. EtOH was evaporated, the aq. soln. acidified with conc. HCl to pH 2, and the product extracted with $Et_2O$. After evaporation of the org. phase and drying, a white powder resulted: 41.5 g (74%). M.p. 61–64° ([11]: 37–39°). IR (KBr): 1690 (CO). $^1$H-NMR ($(D_6)$acetone): 1.95 (*quint.*, 2 H, $CH_2CH_2CH_2$); 2.75 (*t*, 4 H, $SCH_2CH_2$); 3.25 (*s*, 4 H, $SCH_2CO$).

*Cyclic Amides: General Procedure.* The diacyl chlorides were prepared by reaction of the appropriate dicarboxylic acid (0.05 mol) with $SOCl_2$ (*puriss.*, 0.80 mol). After complete dissolution, the mixture was stirred at 40° for 1 h, the excess $SOCl_2$ distilled off at 11 Torr, and the residue treated 3 times with toluene (50 ml), which was distilled off to remove the last traces of $SOCl_2$. The residual oil was kept under $N_2$ at 4° and then directly used for the cyclization procedure.

The cyclization was performed using a high-dilution apparatus (*Normag AG*) under dry $N_2$ at −10° to 0°. To toluene (1 l), the toluene solns. (500 ml) of the diacyl chloride (0.05 mol) and of the diamine (0.10 mol) were simultaneously and dropwise added at a rate of *ca.* 1 ml/min. After complete addition, the two dropping funnels were rinsed with dry toluene (50 ml). The mixture was then filtered and the solid extracted several times with $CH_2Cl_2$. The product of the $CH_2Cl_2$ phase (dried and evaporated) was combined with that of the evaporated toluene phase from the reaction to give the crude product. In the case of **5**, all of the product was dissolved in the toluene phase so that the solid was discarded. The crude products were purified by FC (silica gel, $CH_2Cl_2$/MeOH 10:1), except for **5** which was already anal. pure. *Table 1* gives a summary of the reactions and their yields.

Table 1. *Experimental Conditions for the High-Dilution Cyclization*

| Diacid | Diamine | Product | Yield [%] |
|---|---|---|---|
| **1** | *N*-methylethane-1,2-diamine | **2** | 27 |
| **4** | *N*-methylethane-1,2-diamine | **5** | 52 |
| **7** | *N*-methylpropane-1,3-diamine | **8** | 59 |

*7-Methyl-1,4-dithia-7,10-diazacyclododecane-6,11-dione* (**2**). IR (KBr): 3285 (NH), 2925 (CH), 1670, 1630 (CON). Anal. calc. for $C_9H_{16}N_2O_2S_2$: C 43.52, H 6.49, N 11.28, S 25.82; found: C 43.59, H 6.35, N 11.20, S 25.84.

*8-Methyl-1,5-dithia-8,11-diazacyclotridecane-7,12-dione* (**5**). IR (KBr): 3315 (NH), 2920, 2855 (CH), 1670, 1630 (CON). $^{13}$C-NMR ($CDCl_3$): 27.55, 31.05 ($SCH_2CH_2$); 31.35 ($CH_2CH_2CH_2$); 33.45 ($CH_2NH$); 35.35 (MeN); 36.70, 39.35 ($SCH_2CO$); 44.95 ($MeNCH_2$); 169.85, 172.15 (CO). Anal. calc. for $C_{10}H_{18}N_2O_2S_2$: C 45.77, H 6.91, N 10.68, S 24.44; found: C 45.52, H 6.89, N 10.46, S 24.41.

*9-Methyl-1,5-dithia-9,13-diazacyclohexadecane-8,14-dione* (**8**). IR (KBr): 3255 (NH), 2930 (CH), 1640 (CON). $^{13}$C-NMR ($CDCl_3$; two conformations): 26.25, 26.40, 27.55, 28.20, 28.30, 28.40, 28.60, 29.00, 29.75, 30.30, 30.45, 31.05, 33.05, 34.45, 35.00, 36.20, 36.50, 38.40, 44.75, 47.80 ($CH_2$); 33.30, 35.25 (MeN); 171.15, 171.45, 171.70, 172.35 (CO). Anal. calc. for $C_{13}H_{24}N_2O_2S_2$: C 51.28, H 7.94, N 9.20, S 21.06; found: C 51.28, H 8.18, N 9.15, S 20.78.

*Reduction of the Cyclic Amides: General Procedure.* A suspension of the pure cyclic diamide (8–14 mmol) in diethyleneglycol dimethyl ether (100–200 ml) was purged with $N_2$ (1 h), treated with 1M diborane (120–180 mmol)

in THF at r.t. then boiled under reflux. After 6–7 h, the soln. was cooled to r.t., treated again with 1M diborane (100–150 mmol) in THF, and boiled under reflux for 17–18 h. After repeating this treatment for a 3rd time (1M diborane (80–120 mmol) in THF, 3 h boiling under reflux), the excess of diborane was destroyed by addition of MeOH (100–150 ml). The clear soln. was evaporated, the residue taken up with MeOH/$H_2O$/conc. HCl soln. 80:40:16, and boiled under reflux overnight. The soln. was evaporated, the residue treated with 6M KOH and extracted several times with $CH_2Cl_2$, the org. phase dried ($Na_2SO_4$) and evaporated, and the crude product purified by FC (silica gel, MeOH/25% $NH_3$ soln. 20:0.3 for **3** and **6**, MeOH/$CH_2Cl_2$/25% $NH_3$ soln. 18:2:0.5 for **9**): 91% of **3**, 83% of **6**, and 71% of **9**.

*7-Methyl-1,4-dithia-7,10-diazacyclododecane* (**3**). IR (film): 3255 (NH), 2910, 2790 (CH). $^{13}$C-NMR ($CDCl_3$): 30.15, 31.05 ($SCH_2CH_2N$); 32.25, 33.05 ($SCH_2CH_2S$); 42.85 (MeN); 46.65, 47.90, 56.20, 56.85 ($CH_2N$). Anal. calc. for $C_9H_{20}N_2S_2$: C 49.05, H 9.15, N 12.71, S 29.10; found: C 48.86, H 9.02, N 12.48, S 29.33.

*8-Methyl-1,5-dithia-8,11-diazacyclotridecane* (**6**). IR (film): 3290 (NH), 2915, 2790 (CH). $^{13}$C-NMR ($CDCl_3$): 29.15, 30.15, 30.80, 31.70 ($SCH_2$); 33.70 ($CH_2CH_2CH_2$); 42.25 (MeN); 46.85, 47.25, 57.55, 59.90 ($CH_2N$). Anal. calc. for $C_{10}H_{22}N_2S_2$: C 51.23, H 9.46, N 11.95, S 27.36; found: C 51.08, H 9.43, N 11.82, S 27.29.

*9-Methyl-1,5-dithia-9,13-diazacyclohexadecane* (**9**). IR (film): 3285 (NH), 2940, 2790 (CH). $^1$H-NMR ($CDCl_3$): 1.70, 1.75, 1.80, 1.90 (*quint.*, 8 H, $CH_2CH_2CH_2$); 2.20 (*s*, MeN); 2.40, 2.60, 2.65, 2.75 (*t*, 16 H, $CH_2CH_2X$). $^{13}$C-NMR ($CDCl_3$): 26.75, 27.90 ($SCH_2CH_2CH_2N$); 29.45, 29.55 ($SCH_2CH_2CH_2S$); 29.80, 30.50, 30.55 ($CH_2CH_2CH_2$); 42.40 (MeN); 48.40, 48.90, 56.65, 56.90 ($CH_2N$). Anal. calc. for $C_{13}H_{28}N_2S_2 \cdot 0.2\ H_2O$: C 55.74, H 10.22, N 10.00, S 22.89; found: C 55.82, H 10.05, N 10.23, S 22.82.

*10-Methyl-1,4-dithia-7,10-diazacyclododecane-7-acetonitrile* (**11**). A soln. of 35% formaldehyde (4.21 ml, 53.1 mmol) was given to a suspension of **3** (2.34 g, 10.62 mmol) in $H_2O$ (20 ml) at 0°. Addition of AcOH (8.4 ml) gave a clear soln. which was reacted with KCN (3.46 g, 53.11 mmol) in $H_2O$ (20 ml). After stirring for 1 h at r.t., the mixture was treated with solid KOH and then extracted 5 times with $CH_2Cl_2$. The org. phase was dried and evaporated and the crude product submitted to FC (silica gel, MeOH): pure **11** (2.58 g, 94%). IR (film): 2915, 2795 (CH), 2230 (CN). $^{13}$C-NMR ($CDCl_3$): 28.80, 29.15 ($SCH_2CH_2N$); 31.55, 31.75 ($SCH_2CH_2S$); 42.60 (MeN); 43.15 ($NCH_2CN$); 51.30, 55.45, 56.10, 59.15 ($CH_2N$); 115.10 ($CH_2CN$). Anal. calc. for $C_{11}H_{21}N_3S_2$: C 50.93, H 8.16, N 16.20, S 24.72; found: C 50.87, H 8.14, N 16.15, S 24.46.

*10-Methyl-1,4-dithia-7,10-diazacyclododecane-7-ethanamine* (**12**). *Raney*-Ni (2.5 g) was added to **11** (950 mg, 3.66 mmol) in dry EtOH (40 ml). The soln. was cooled, treated with liq. $NH_3$, and hydrogenated at 100 atm for 20 d in the autoclave. The catalyst was filtered off and the solvent evaporated. After adding 1M NaOH (20 ml) and KCN (2 g), the crude product was extracted with $CH_2Cl_2$ (5 times). The org. phase was dried ($Na_2SO_4$) and evaporated and the residue submitted to FC (silica gel, MeOH/25% $NH_3$ soln. 15:1): pure **12** (562.7 mg, 58%). IR (film): 3360 (NH), 2950, 2790 (CH). $^1$H-NMR ($CDCl_3$): 1.60 (br., $NH_2$); 2.20 (*s*, MeN); 2.50, 2.65, 2.80, 2.95, 3.05 (*m*, 20 H, $CH_2X$). $^{13}$C-NMR ($CDCl_3$): 28.20, 28.85 ($SCH_2CH_2N$); 31.10, 31.95 ($SCH_2CH_2S$); 39.85 ($CH_2NH_2$); 42.65 (MeN); 52.10, 56.10, 56.80, 58.55, 59.85 ($CH_2N$). FAB-MS: 264 ($M^+$).

For the preparation of **12**·3 HBr, 47% HBr soln. was added to the colorless oil **12** in MeOH, and the solvent was evaporated. Anal. calc. for $C_{11}H_{25}N_3S_2 \cdot 3\ HBr \cdot 1.2\ H_2O$: C 25.03, H 5.81, Br 45.41, N 7.96, S 12.15; found: C 25.37, H 5.72, Br 45.14, N 7.87, S 11.96.

*10-Methyl-1,4-dithia-7,10-diazacyclododecane-7-acetic Acid* (**13**). Nitrile **11** (602 mg, 2.32 mmol) was boiled under reflux in 36% HCl soln. (40 ml) for 7 h. The crude product was purified with FC (silica gel, MeOH/$H_2O$/25% $NH_3$ soln. 15:5:0.1): **13** (586.2 mg, 91%). IR (film): 3395 (NH, OH), 2960 (CH), 1735 (CO). $^{13}$C-NMR ($D_2O$): 33.95, 37.75 ($SCH_2CH_2N$); 38.15, 40.35 ($SCH_2CH_2S$); 47.50 (MeN); 57.85, 60.85, 61.90, 64.15 ($SCH_2CH_2N$); 62.30 ($CH_2COOH$); 185.40 (COOH). FAB-MS: 279 ($M^+$).

For the preparation of the hydrochloride, 1M HCl was added to the colorless oil **13** in MeOH, and the solvent was evaporated. Anal. calc. for $C_{11}H_{22}N_2O_2S_2 \cdot 2.4\ HCl \cdot 0.8\ H_2O$: C 34.74, H 6.89, Cl 22.37, N 7.36, S 16.86; found: C 35.00, H 6.66, Cl 22.25, N 7.33, S 16.75.

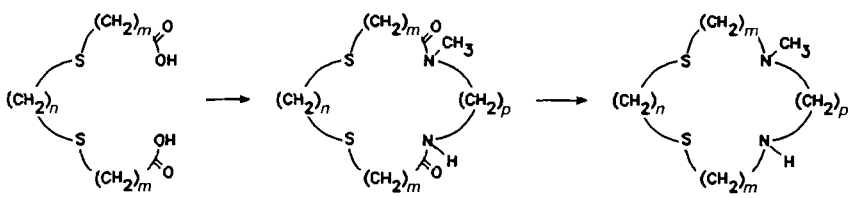
*Potentiometric Measurements.* All solns. were prepared with bidistilled $H_2O$. Titrations were carried out with the automatic titrator described previously [12], consisting of a *Metrohm-605* potentiometer, a *Metrohm-655* dosimat with a combined glass electrode and an *AT-286* computer at 25.0 ± 0.1°, under $N_2$, using 0.4M NaOH as titrant. The buffer solns. (pH 4.00 and 7.00) for calibration were also from *Metrohm*. Experimental conditions: $I = 0.5$ ($KNO_3$), $[L]_{tot} = 2.5–3.0 \cdot 10^{-3}$ M and $[Ag^+]_{tot}$ was 90% and 50% of $[L]_{tot}$. In general, 70 to 100 exper. points between pH 2.5 and 11.5 were registered for each titration curve. In addition, the concentration of the free $Ag^+$ ion was determined at the beginning of each titration using an Ag electrode, calibrated against three solns. with known $[Ag^+]$.

*Stability in Blood Serum.* To test the blood-serum stability, 2 µl of $^{110m}$Ag ($\gamma$-emitter, $T_{½}$ 253 d) complex solns. ($[L]_{tot} = 6 \cdot 10^{-4}$ M, $[L]_{tot}/[Ag]_{tot}$ either 1:0.9 or 1:0.1) were mixed with 198 µl of blood serum and 800 µl of buffer

(0.1M $NH_4OAc$ pH 6.73, or 0.1M *Tris*/$HNO_3$ pH 9.00). After 10 min incubation time, the soln. was centrifugated (*Heraeus Sepatech 2.0 RS*) for *ca.* 5 h in a 'microsep' (*Ultracent-10, Bio Rad*) able to separate substances with mol.wt. > 10000. The upper and lower phase were taken up in buffer and measured in a *Packard-A-5000-D* $\gamma$-counter. In all experiments, the radioactive $Ag^+$ was found in the upper phase together with the proteins of the blood. To test the method, the same experiments without blood serum were also run. The $Ag^+$ complex was always found in the lower phase.

**Results and Discussion.** – *Syntheses.* The synthesis of the $N_2S_2$-macrocycles **3**, **6**, and **9** follows the procedure described in [9]. The dicarboxylic acids **1**, **4**, and **7** are converted to the diacyl chlorides with $SOCl_2$ and reacted with the double molar amount of *N*-methylethane-1,2-diamine or *N*-methylpropane-1,3-diamine in toluene under high-dilution conditions (→ **2**, **5**, and **8**, resp.; *Scheme 1*). Then, the cyclic diamides are reduced with diborane in THF to the target diamines, whereby for a complete reduction and good yields a large molar excess of diborane is needed. The boramine adducts are hydrolyzed with HCl in $H_2O$/MeOH and the final products extracted from alkaline solution with $CH_2Cl_2$ and purified by flash chromatography.

*Scheme 1*



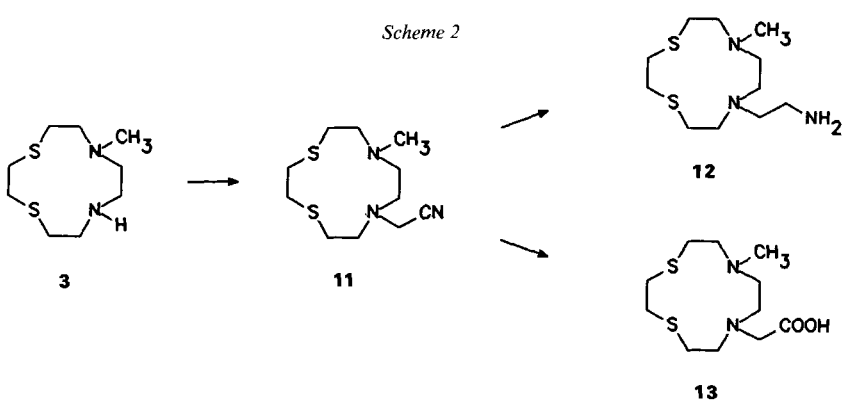
**1** $n = 2, m = 1$
**4** $n = 3, m = 1$
**7** $n = 3, m = 2$

**2** $n = 2, m = 1, p = 2$
**5** $n = 3, m = 1, p = 2$
**8** $n = 3, m = 2, p = 3$

**3** $n = m = p = 2$
**6** $n = 3, m = p = 2$
**9** $n = m = p = 3$
**10** $n = p = 2, m = 3$

The choice of the *N*-methyl-substituted diamine components allows the selective introduction of one side chain at the secondary N-atom of the macrocycles. Thus, the reaction of **3** under the conditions of the *Strecker* synthesis gives the acetonitrile derivative **11** (*Scheme 2*). The nitrile group is then reduced to an amino function to give **12** or hydrolyzed to the carboxylic acid **13**.

*Scheme 2*



**3** **11** **12** **13**

The ligands so prepared allow to systematically study the influence of the ring size and of additional donor groups in the side chain on the stability of their $Ag^+$ complexes and then test the possibility to use them for labelling monoclonal antibodies.

*Potentiometric Titrations.* The pH titrations of the ligands in absence or presence of $Ag^+$, evaluated with the program TITFIT [13], gave the stability constants $\beta_{xyz}$ (*Eqn. 1*), in

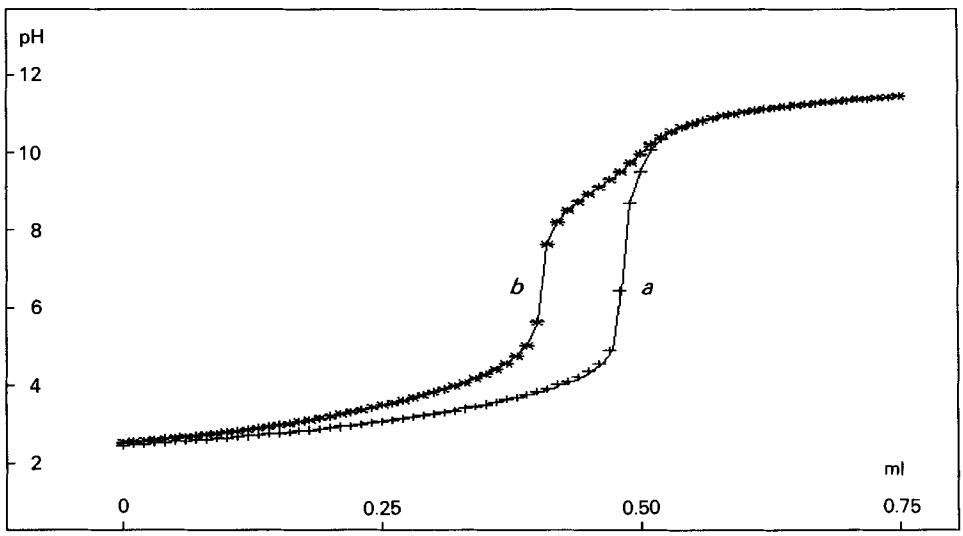



Fig. 1. *pH Titrations of ligand* **3** *in the presence of* $Ag^+$: $[L]_{tot} = 3.03 \cdot 10^{-3}$ M *with* a) $[Ag^+]_{tot} = 2.72 \cdot 10^{-3}$ M *and* b) $[Ag^+]_{tot} = 1.49 \cdot 10^{-3}$ M

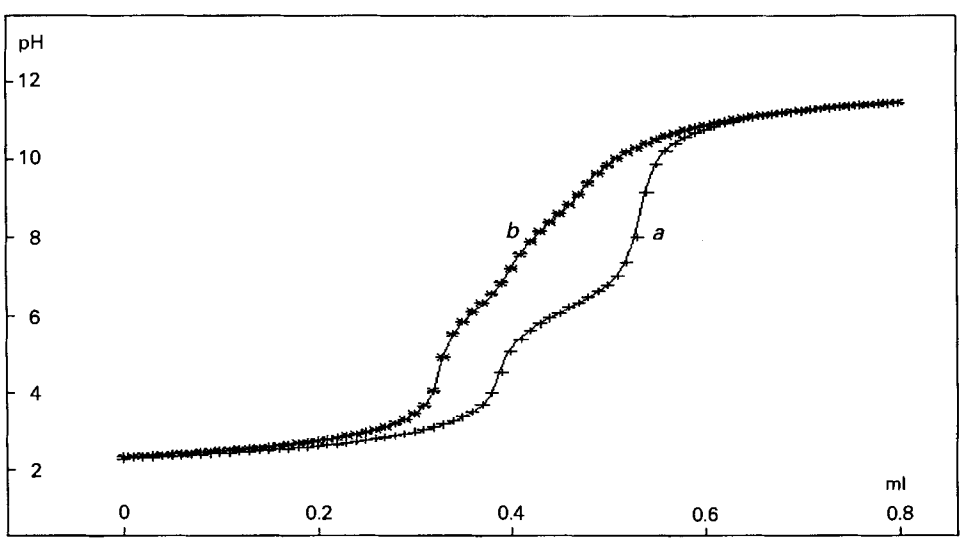



Fig. 2. *pH Titrations of ligand* **12** *in the presence of* $Ag^+$: $[L]_{tot} = 2.49 \cdot 10^{-3}$ M *with* a) $[Ag^+]_{tot} = 2.25 \cdot 10^{-3}$ M *and* b) $[Ag^+]_{tot} = 1.24 \cdot 10^{-3}$ M

which $a_H$ represents the proton activity. Examples of titrations showing the quality of the fitting are given in *Figs. 1* and *2*.

$$\beta_{xyz} = \frac{[M_xL_yH_z]}{[M]^x \cdot [L]^y \cdot a_H^z} \quad (1)$$

The first protonation constants $pK_{a1}$ (*Table 2*) have values typical for a secondary or tertiary amine. The tendency of increasing $pK_{a1}$ with increasing ring size is probably due to the fact that the larger rings are more accessible for protons, since internal H-bonds are weaker and/or the solvation is different. This trend was previously observed for the unsubstituted macrocycles [14]. The second protonation constants change drastically with ring size, or better with the mean distance between the two N-atoms, and this is clearly determined by electrostatic interactions.

Table 2. *Acid-Dissociation Constants for $N_2S_2$-Ligands and Formation Constants of Their $Ag^+$ Complexes at 25° ● 0.1°. $I = 0.5$ ($KNO_3$).*

| | Ligand | | | | | |
|---|---|---|---|---|---|---|
| | **3** | **6** | **10** | **9** | **12** | **13** |
| $pK_{a1}$ | 9.25 (1) | 9.39 (1) | 9.83 (1) | 10.17 (1) | 10.37 (1) | 10.33 (1) |
| $pK_{a2}$ | 4.30 (1) | 4.33 (1) | 5.05 (1) | 7.52 (1) | 8.37 (1) | 3.73 (1) |
| $\log\beta_{110}$ | 10.95 (1) | 10.06 (1) | 8.08 (1) | 7.28 (1) | 14.43 (1) | 12.32 (1) |
| $\log\beta_{111}$ | 14.40 (1) | 13.72 (1) | 14.36 (1) | 14.83 (1) | 20.56 (1) | 16.53 (1) |
| $\log\beta_{112}$[a]) | 16.446 | 16.554 | 18.628 | 21.548 | 22.418 | 18.329 |
| $\log\beta_{120}$ | 14.11 (5) | 12.58 (9) | 10.24 (3) | – | – | – |
| $\log\beta_{121}$ | 22.65 (6) | – | – | – | – | – |
| $\log\beta_{122}$ | – | – | 26.90 (1) | 27.30 (4) | – | – |

[a]) These values were kept fixed in the fitting procedures.

The ligands **12** and **13** with an additional donor group in their side chain have also two protonation constants above 2.5, the third being too low to be determined by pH titrations. The relatively high value $pK_{a2}$ for **12** is due to the protonation of the side chain and one ring N-atom, which are far apart, so that the electrostatic repulsion is minimized. The second protonation of **13** with $pK_{a2} = 3.73$ probably takes place at the carboxylate group.

The determination of the stability constants of the $Ag^+$ complexes by pH titrations is difficult, because at low pH, the complex $[AgLH_2]^{3+}$ is already formed. Since no protons are released in this complexation step, it is not possible to determine the relative distribution between $Ag^+$ and $[AgLH_2]^{3+}$ by pH measurements. We, therefore, additionally used potentiometric measurements with an Ag electrode which allows to measure the concentration of the free $Ag^+$ ion. From such measurements, the stability constants $\beta_{112}$ were calculated and kept fixed in the fitting of the pH titrations, from which the remaining stability constants were determined (*Table 2*).

All ligands form 1:1 species ($[AgLH_2]^{3+}$, $[AgLH]^{2+}$, $[AgL]^+$), whereas 1:2 complexes are observed only in certain instances and are completely absent for the two functionalized ligands **12** and **13** (*Figs. 3–5*).

A closer look at the values reveals that the stability $[AgL]^+$ increases with decreasing ring size, the most stable complex being formed by the 12-membered ring **3**. The ring size also is important for the protonation of $[AgL]^+$ to $[AgLH]^{2+}$ and $[AgLH_2]^{3+}$. The larger the ring, the easier it is to add protons. This can be understood, as in the case of the protonation of the ligands, by a decreasing coulombic repulsion between the positive

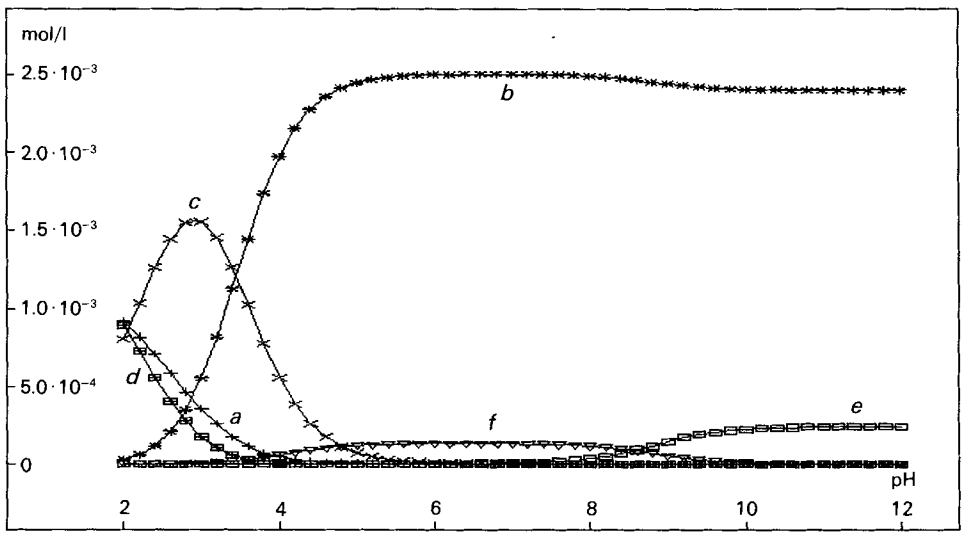



Fig. 3. *Species distribution of a solution containing ligand* **3** ($[L]_{tot} = 3.03 \cdot 10^{-3}$ M) *and* $Ag^+$ ($[Ag^+]_{tot} = 2.72 \cdot 10^{-3}$ M). *Species:* a) $[Ag]^+$, b) $[AgL]^+$, c) $[AgLH]^{2+}$, d) $[AgLH_2]^{3+}$, e) $[AgL_2]^+$, *and* f) $[AgL_2H]^{2+}$.

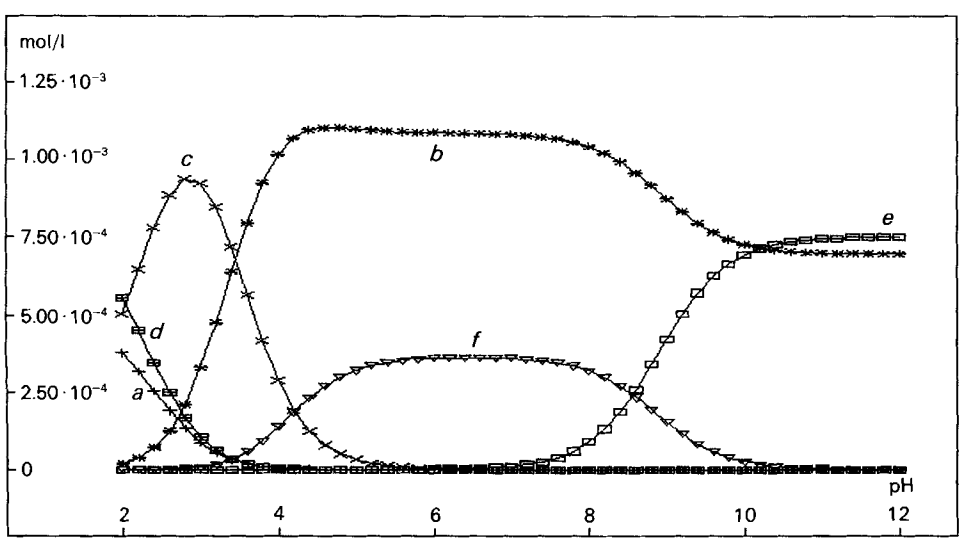



Fig. 4. *Species distribution of a solution containing ligand* **3** ($[L]_{tot} = 3.03 \cdot 10^{-3}$ M) *and* $Ag^+$ ($[Ag^+]_{tot} = 1.49 \cdot 10^{-3}$ M). *Species:* a) $[Ag]^+$, b) $[AgL]^+$, c) $[AgLH]^{2+}$, d) $[AgLH_2]^{3+}$, e) $[AgL_2]^+$, *and* f) $[AgL_2H]^{2+}$.

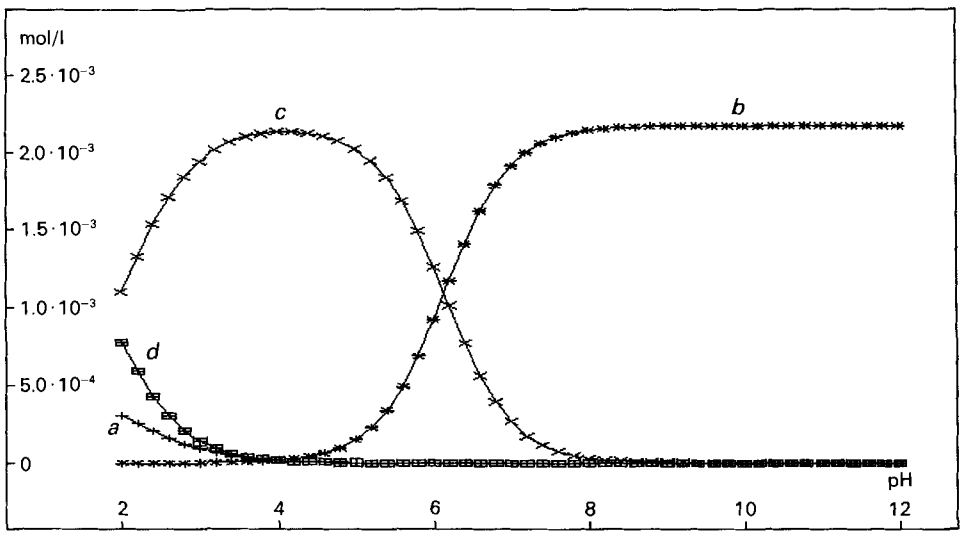



Fig. 5. *Species distribution of a solution containing ligand* **12** ($[L]_{tot} = 2.49 \cdot 10^{-3}$ M) *and* $Ag^+$ ($[Ag^+]_{tot} = 2.25 \cdot 10^{-3}$ M). *Species:* a) $[Ag]^+$, b) $[AgL]^+$, c) $[AgLH]^{2+}$, *and* d) $[AgLH_2]^{3+}$.

charges. The observation that protonated species are formed is a clear indication, that $Ag^+$ strongly binds to the thioether group, even without the coordination of the amino donors. Similarly, the existence of 1:2 complexes reveals, that $Ag^+$ is coordinatively unsaturated, especially when the ligand is protonated at one or both of the N-donors. For $[AgL_2]^+$, the same trend as for $[AgL]^+$ is observed: the smaller the ring size, the more stable the complex.

The two ligands with a pendant side chain also form $[AgL]^+$, $[AgLH]^{2+}$, and $[AgLH_2]^{3+}$, but no 1:2 species. In addition, the stability of the $[AgL]^+$ complex becomes higher than those of nonfunctionalized rings, the highest value $\log\beta_{110} = 14.43$ being obtained with the ethanamine side chain. To our knowledge, there is no complex with a $N_xS_y$ ligand in the literature exhibiting a larger stability than **12**. So the $Ag^+$ complexes of 4,10-dimethyl-1,7-dithia-4,10-diazacyclododecane [15] and of 1,10-dithia-4,7,13,16-tetraazacyclooctadecane [16] have stability constants of 11.5 and 10.4, respectively.

The question about the structure of the species found by equilibrium measurements in solution is difficult to answer. In $[AgLH_2]^{3+}$, one must assume that $Ag^+$ is only bound by the thioether S-atoms since the two amino groups are protonated and thus cannot coordinate. When the protons are removed ($[AgLH]^{2+}$ and $[AgL]^+$), the chance of N-participation in the coordination of $Ag^+$ increases. In the structure of the crystalline $Ag^+$ complex with **3**, one of the $Ag^+$ is coordinated by the 12-membered macrocycle through two N- and two S-atoms in a square-pyramidal geometry [17]. Probably, this structure remains intact in solution for $[AgL]^+$. The observation that in the solid $[AgL]^+$ is pentacoordinated was decisive for preparing ligands with a pendant donor group which can block the fifth coordination side. The finding that the stability of the complexes increases when a donor group is introduced into the side chain is a good evidence for pentacoordination of $Ag^+$, even in solution.

All $Ag^+$ complexes of the $N_2S_2$ macrocycles were tested in blood serum for their stability, but all exchanged the metal ion within 10 min. This indicates that the thermodynamic stability is not high enough to prevent transmetallation under physiological conditions.

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